The immunology of infection

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Abstract

When micro-organisms invade, conserved pattern recognition receptors activate innate defences including phagocytes, cytokines and complement followed by acquired immune responses mediated by T cells and B cells. Many pathogens have evolved specific mechanisms that enable them to evade host defences. An increasing number of individual human genes that influence the outcome of specific infections have been identified. Deficiency of specific components of the immune system (as a result of either genetic or acquired disorders) can predispose to characteristic patterns of infection. The immune response may also contribute to the pathogenesis of infectious disease as a result of excessive cytokine production or immune complex formation.

Keywords antibody; B cell; cytokine; innate; macrophage; MHC; T cell

Infections have exerted a strong selective pressure on the evolution of the human immune system, the different components of which have evolved to resist infection by particular micro-organisms. An increasing number of individual human genes that influence the outcome of specific infections have been identified. Deficiency of specific components of the immune system (as a result of either genetic or acquired disorders) can predispose to characteristic patterns of infection. The immune response may also contribute to the pathogenesis of infectious disease.

Innate defences

Innate responses are particularly important early in the course of an infection. They involve rapid recruitment and activation of soluble proteins or pre-existing cells without requiring cell division. Cells such as macrophages and dendritic cells express a limited repertoire of invariant germline-encoded pattern recognition receptors (including the Toll-like receptors) that recognize a few highly conserved, distinctive biochemical structures present in many micro-organisms (such as bacterial lipopolysaccharide (LPS), teichoic acids, yeast cell wall mannans, dsRNA). Innate responses triggered by these pattern recognition receptors often activate acquired immune responses and influence the appropriate type of T cell response. Many vaccine adjuvants increase T cell and/or B cell responses against foreign proteins by activating pattern recognition receptors on dendritic cells. Mutations in a given pattern recognition receptor can increase susceptibility to a specific pathogen. Toll-like receptor 5 (TLR-5) normally recognizes bacterial flagellin, but a genetic stop codon polymorphism that abolishes TLR-5 function confers increased susceptibility to Legionnaire's disease caused by the flagellate bacterium *Legionella pneumophila*.[1]

Defensins are a family of small, cysteine-containing antimicrobial peptides. These positively charged polar molecules insert into and disrupt microbial cell membranes, which have a higher content of negatively charged phospholipids than human cell membranes. α-defensins are produced by neutrophils and intestinal Paneth cells. β-defensins are produced by epithelial cells of the kidney, pancreas, skin and respiratory tract in response to microbial invasion or exposure to bacterial LPS or tumour necrosis factor α (TNFα). In addition to their antimicrobial action, both α-defensins and β-defensins chemoattract memory T cells to sites of infection; β-defensins also attract immature dendritic cells, which then take up antigen and migrate to regional lymph nodes to initiate acquired immune responses.

Complement proteins are present in plasma and constitute an enzyme cascade that can attack micro-organisms through:

- the alternative complement pathway. Bacterial or yeast cell walls activate C3bBb which cleaves C3
- the classical pathway. Immune complexes of antigen bound by specific IgM or IgG bind to C1q which activates C4 and C2 to produce C4b2b which cleaves C3. Other activators of the classical pathway are C-reactive protein (which binds to phosphocholine residues in bacterial cell walls and activates C1q) and mannose-binding lectin (which binds to microbial carbohydrates and triggers cleavage of C4 and C2). Specific genotypes of mannose-binding lectin are associated with increased susceptibility to invasive pneumococcal disease.[2]

Both pathways lead to deposition of C3. Deposition of C3b on micro-organisms opsonizes them for phagocytosis by neutrophils which are attracted by C5a. Deposition of C3d greatly enhances the uptake and presentation of microbial antigen by antigen-specific B cells, and so potentiates the development of a strong antibody response. Genetic deficiency of C3 is associated with severe bacterial infections. Deficiency of the terminal components C5–9 is associated specifically with *Neisseria* infections.

Interferons: the three types of interferon (IFN) (α, β and γ) were originally described for their antiviral effect, but are now recognized to have many other actions (e.g. inhibiting cell proliferation, regulating immune responses). Viral infections induce production of IFN-α and IFN-β in a wide variety of cell types. IFN-α and IFN-β are released from virus-infected cells and bind to a specific surface receptor on neighbouring uninfected cells, inducing production of the protein kinase, dsRNA-activated inhibitor of translation (DAI). In the presence of double-stranded viral RNA, DAI phosphorylates and inactivates a cellular protein (eIF-2a) required for translation of mRNA, thereby inhibiting protein synthesis in any cell that becomes infected. The antiviral state induced by IFN-α/β is an important host defence; mice lacking the surface receptor for IFN-α/β are extremely susceptible to lethal infection when exposed to very small doses of virus. IFNs are used as antiviral agents, in cancer therapy and in multiple sclerosis, although dose-dependent side effects are common. IFN-γ is

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a cytokine produced by T cells that activates macrophages and natural killer (NK) cells.

Neutrophils are produced in large numbers (10^{11} per day) and circulated for only a few hours before passing through capillary walls into the extravascular space. Neutrophils are highly efficient phagocytes of bacteria and fungi. Following phagocytosis, ingested organisms are killed by multiple mechanisms including production of superoxide. A reduction in neutrophil numbers ($<0.5-1 \times 10^9$/l) increases susceptibility to severe bacterial and fungal infections. One-half of all peripheral blood neutrophils are attached to the vascular endothelium and are therefore not measured in the neutrophil count. Factors that alter the adhesiveness of neutrophils can lead to large increases (e.g. glucocorticoids) or decreases in neutrophil count.

Monocytes are derived from the same myeloid precursors and they circulate in the blood for hours to days, then become differentiated tissue macrophages, acquiring specific characteristics dependent on the tissue in which they reside (e.g. liver Kupffer cells, alveolar macrophages). In response to exogenous stimuli (particularly LPS and T cell-derived IFN-γ), macrophages become activated to a state in which their secretion, ingestion and killing are all enhanced.

Secretion — macrophages secrete lysozyme, neutral proteases, interleukin-1 (IL-1), TNFα, superoxide, leukotrienes and complement components.

Ingestion and killing — macrophages can ingest bacteria via the macrophage mannose receptor (which recognizes carbohydrates containing large numbers of mannose residues) or the macrophage scavenger receptor. They also ingest micro-organisms opsonized by IgG and/or complement. The micro-organisms are then killed by oxygen-dependent mechanisms.

Antigen presentation — macrophages present antigen to T cells as processed peptides bound to major histocompatibility complex (MHC) molecules.

Intracellular bacteria and some protozoa preferentially invade macrophages. These organisms include facultative intracellular parasites capable of living outside cells (e.g. *Mycobacterium* spp., *Legionella*, *Listeria*, *Salmonella* spp., *Leishmania*) and obligate intracellular bacteria (e.g. *Rickettsia* spp., *Chlamydia* spp.). *Legionella*, *Salmonella* and *Mycobacterium* can survive and replicate within the phagolysosome. They resist being killed (in a location specifically designed to kill them) by remodelling the phagosome. *Legionella* inhibits fusion of the phagosome with the lysosome, and phagosomes containing mycobacteria show a selective lack of the lysosomal proton-ATPase responsible for normal acidification. Salmonellae carry a gene (*phoP*) that enables them to resist the microbicidal peptides (defensins) present in the lysosomes of neutrophils and macrophages. *Listeria* and some *Rickettsia* spp. avoid being killed by escaping from the phagolysosome into the cytoplasm (*Listeria* by using listeriolysin). However, when infected macrophages have been activated (e.g. by IFN-γ), they become capable of killing intracellular bacteria. The macrophage divalent cation transporter, natural resistance-associated macrophage protein (NRAMP-1), has an important role in macrophage activation. *NRAMP-1* gene mutations increase the susceptibility of mice to a range of intracellular parasites, and certain polymorphisms in the human *NRAMP-1* gene are associated with increased susceptibility to tuberculosis in humans.[3]

Dendritic cells are specialized antigen-presenting cells derived from the myeloid lineage. They circulate through tissues and when activated by inflammatory stimuli, take up antigen and migrate into T cell regions of local lymph nodes. They express high levels of MHC class I and class II molecules and other co-stimulatory molecules (CD80, CD86), and are thus potent antigen-presenting cells for naive T cells. Because they express CD4, dendritic cells are susceptible to infection by HIV.

Cytokines and chemokines

Many mediators are released from monocytes and lymphocytes activated in the immune response (Figure 1). IL-1, IL-6 and TNF-α are released from activated monocytes/macrophages and are inducers of the acute-phase response, causing hepatocytes to increase synthesis of the acute-phase proteins (including antiproteases, haptoglobin, complement components C3, C4 and factor B, fibrinogen, ferritin and, particularly, C-reactive protein and amyloid A protein, which increase 100—1000-fold). Pro-inflammatory cytokines also have a significant role in the pathogenesis of infectious disease.

IL-1 is secreted by macrophages and is a major mediator of the acute-phase response. It is an endogenous pyrogen, inducing fever through direct action on the hypothalamus associated with locally increased synthesis of prostaglandin E2. IL-1 also has effects on endothelial cells, including increased synthesis of prostaglandins E2 and I2, increased production of a plasminogen activator inhibitor, and increased expression of intercellular adhesion molecule-1, which probably explains the increased adherence of circulating mononuclear cells to endothelia induced by IL-1. The net effect of these actions is to decrease blood flow and promote local coagulation, which may occur in endotoxin shock.

TNF-α induces an acute-phase response and fever, and induces release of IL-1, which also produces fever. TNF also has direct effects on endothelial cells similar to those of IL-1, and has antiviral effects synergistic with those of the interferons. TNF is probably a major mediator in endotoxin shock and severe falciparum malaria. Specific polymorphisms in the promoter of the human TNF gene are associated with increased severity of falciparum malaria.

Chemokines (chemoattractant cytokines) are a family of small polypeptides which coordinate the migration of leucocytes from the circulation into different tissues, including sites of inflammation. They comprise:

- α (CXC) — attracts and activates neutrophils (e.g. IL-8)
- β (CC) — attracts monocytes and lymphocytes (e.g. RANTES)
- γ (C) — attracts lymphocytes (e.g. lymphotactin).

Chemokines act by binding to a family of G protein-coupled 7 transmembrane glycoprotein receptors that are expressed on leucocytes; many chemokine receptors can be activated by more than one chemokine. Naïve human CD4+ T cells express CXCR4 and CCR7, which favour recirculation through lymph nodes that secrete the corresponding chemokines CCL19 (ELC) and CCL21 (SLC). In contrast, many activated CD4+ T cells express CCR5 but not CXCR4 or CCR7, favouring their migration out of lymph nodes and into inflamed tissues where activated macrophages secrete (CCL3) MIP-1α, (CCL4) MIP-1β and (CCL5) RANTES. Some micro-organisms exploit chemokine receptors to enter cells. Different strains of HIV use chemokine receptors CCR5

